REMARKS

Status of the Claims.

Claims 1-12, 14-17, and 71 are pending with entry of this amendment. Claims 1, 6, 9, and 11 are amended herein. Claim 1 has been amended to more precisely define the CYP24 gene as one that is amplified using SEQ ID NOs: 1 and 2 as amplification primers. Support for this amendment is found in the specification at least at page 53, lines 11-17, taken with page 54, Table 1. The remaining amendments conform the claims to the preamble of claim 1 and clarify that the method relates to detecting a breast cancer marker. Support for the amendments is found at least at page 20, lines 6-9. Claim 33, which was added in the last Amendment, should have been designated claim 71, as the application was originally filed with 70 claims. This oversight has been corrected above. Therefore, these amendments introduce no new matter.

Objection to the Specification.

The Examiner objected to the specification as failing to provide proper antecedent basis for the claimed subject matter. Office Action, page 2. Specifically, the Examiner contends that there is no antecedent basis in the specification for "the **endogenous** vitamin D hydroxylase (*CYP24*) gene." As this language has been deleted from the pending claims, withdrawal of the objection to the specification is respectfully requested.

Rejection Under 35 U.S.C. § 112, Second Paragraph.

Claims 1-12, 14-17, and 33 (now 71) were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because, according to the Examiner, claim 1 lacked antecedent basis for "the endogenous vitamin D 24 hydroxylase . . . ." Office Action, page 6. This phrase has been replaced by the phrase "a vitamin D 24 hydroxylase (*CYP24*) gene that can be amplified using amplification primers, wherein one primer comprises SEQ ID NO: 1 and another primer comprises SEQ ID NO: 2." As the rejection is now moot, withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph.

Written Description

Claims 1-12, 15-17, and 33 (now 71) were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Office Action, page 3. This rejection is respectfully traversed.

The first basis for the rejection is that the phrase "the **endogenous** vitamin D 24 hydroxylase (*CYP24*) gene" represents new matter. Applicants respectfully submit that the endogenous gene was the subject of the copy number determination in Example 1, and the specification is replete with references to detecting CYP24 level in a biological sample from an animal and comparing the level in a control sample taken from a normal, cancer-free animal. *See, e.g.*, page 20, lines 6-14. As one of skill in the art readily appreciates, the *CYP24* gene in test sample or a control sample from a normal animal is the endogenous gene. Nevertheless, in the interest of expediting prosecution, Applicants have amended claim 1 to delete the reference to the endogenous gene and to recite "a vitamin D 24 hydroxylase (*CYP24*) gene that can be amplified using amplification primers, wherein one primer comprises SEQ ID NO: 1 and another primer comprises SEQ ID NO: 2." Explicit support for this language is found at least at page 53, lines 15-17. This passage recites that expression levels of *CYP24* were analyzed by RT-PCR using the primers listed in Table 1. RT-PCR measures mRNA levels by reverse transcribing the mRNA and amplifying the target nucleic acid sequences with primers. The mRNA sequence is also present in the genomic DNA sequence, so the primers define both the mRNA and the gene corresponding to the target nucleic acid sequences. Thus, identifying the *CYP24* gene as that which is "amplified using amplification primers, wherein one primer comprises SEQ ID NO: 1 and another primer comprises SEQ ID NO: 2" unambiguously identifies the *CYP24* gene that is the subject of the claimed method.

The second basis for the rejection is that "'endogenous *CYP24*' still encompasses a genus of molecules that are not necessarily the wild type forms of *CYP24*." Office Action, page 4. This statement is not understood. The term "wild type" is typically used to refer to a naturally occurring form of a gene, as opposed to one in which mutations have been introduced by a scientist. The claimed method relates to the detection of CYP24 nucleic acid (DNA or mRNA), protein, or activity in a biological sample from a human. The *CYP24* gene in such a sample is the naturally occurring *CYP24* gene, not a gene into which mutations have been introduced by a scientist.

The Examiner goes on to state that "'endogenous *CYP24*' . . . reads on a plethora of variant, mutated and alternate forms of *CYP24*." *Id.* It is true that a subject might carry a *CYP24* that has a mutation not found in the majority of the population and that the claims encompass detecting levels of the mutant *CYP24*, as well as the levels of the *CYP24* that is the predominant form. However, the claims now recite that the *CYP24* gene is "a vitamin D 24 hydroxylase (*CYP24*) gene that can be amplified using amplification primers, wherein one primer comprises SEQ ID NO: 1 and another primer comprises SEQ ID NO: 2." All members of this genus share the common feature of appropriate binding sites for the recited primers. This feature distinguishes the *CYP24* gene to be detected from other genes. That members of the genus may differ slightly due, *e.g.*, to allelic variation is of no consequence with respect to the claimed method.

As stated in the M.P.E.P., the "written description requirement for a claimed genus may be satisfied "by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics." M.P.E.P., page 2100-182. In addition to the structural characteristics of binding sites for amplification primers comprising SEQ ID NOs:1 and 2, the genus of nucleic acids defined by "a vitamin D 24 hydroxylase (*CYP24*) gene" must encode a 25-hydroxyvitamin D3 24-hydroxylase enzyme. *See* Applicants' specification at page 7, lines 10-12. These two constraints define, with particularity, the structure of the *CYP24* gene recited in claim 1 and greatly limit the variability between species of *CYP24* genes encompassed by this definition. Accordingly, Applicants submit that the specification meets the M.P.E.P.'s standard for adequate written description of a genus.

The Examiner concluded her written description analysis with the statement that "Applicants have not described *CYP24* with sufficient particularity such that one skilled in the art would recognize that the Applicants had possession of the claimed invention." *Id.* Although Applicants strongly disagree with this position, Applicants have amended the claims to recite the *CYP24* gene with even greater particularity. Applicants actually reduced detection of *CYP24* gene copy number to practice, using the recited primers with four different samples. One of skill in the art would readily appreciate that these primers would amplify all *CYP24* genes that are capable of binding the primers. Accordingly, at the time the application was filed, it would have been possible for Applicants to carry out and describe the amplification of *CYP24* genes from any number of human

samples. Each of the amplification products would correspond to the claimed *CYP24* gene. In other words, Applicants could have actually reduced to practice any number of embodiments in which the amplification products contained minor, *e.g.*, allelic, variations *CYP24* gene nucleotide sequences. However, providing additional examples of performing the claimed method with different samples would have added nothing of import to the description. Accordingly, Applicants submit that one of skill in the art would recognize that Applicants were in possession of the invention as of the time the application was filed. Withdrawal of the § 112 rejection for lack of written description is respectfully requested.

Enablement

Claims 1-12, 14-17, and 33 (now 71) were rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for a method of detecting *CYP24* mRNA in human breast tumor *in vitro* specimens treated with 1,25-dihydroxyvitamin D-3 comprising RT-PCR, [the specification] does not reasonably provide enablement for a method of detecting a predisposition to any cancer comprising detecting the level of *CYP24* nucleic acid or *CYP24* protein in a biological sample and comparing said level with a level from a control sample." Office Action, pages 4-5. This rejection is respectfully traversed.

In response to the statement above that the specification does not enable "detecting a predisposition to **any** cancer," Applicants respectfully point out that the claims unambiguously relate to "detecting a **breast cancer** marker." This leaves the issue of enablement for "detecting the level of *CYP24* nucleic acid or *CYP24* protein in a biological sample." However, the Examiner states that she "does not doubt the ability of one of ordinary skill in the art to detect *CYP24* mRNA and protein levels." *Id.* Presumably, the Examiner also does not doubt the ability of one of skill to detect *CYP24* DNA, especially in view of Example 1, which discusses the use of comparative genomic hybridization (CGH), specifically array CGH, to detect amplification (DNA copy number increases). *See* Applicants' specification, page 52, line 23 – page 53, line 10.

The Examiner's issue is that "Applicant's claims set forth [that] if the target molecule is detected[,] it should be readily presumed one will have breast cancer." Office Action, page 4. Applicants respectfully disagree.

Claim 1 recites "detecting a breast cancer marker." Applicants have amended the body of the claim to conform it to the preamble to avoid any possibility that the claim may be interpreted as requiring a definitive diagnosis based only on detection of an elevated CYP24 level. As those of skill in the art readily appreciate, **a marker of disease tends to indicate** that disease is present or that the subject having the marker is predisposed to develop the disease. **Markers are useful even though many markers do not, by themselves, definitively identify disease presence or predisposition**. Individual markers may be, and typically are, combined with other parameters to arrive at a differential diagnosis.

In the Office Action, the Examiner notes that the Examples include data from established breast cancer cell lines. *Id.* However, in Example 1, Applicants demonstrated by array CGH that "expression of *CYP24* and *VDR* was detected in two breast cancer tumors S21 and S59." Applicants' specification, page 53, lines 20-21. Figure 3 shows that the expression levels in these tumors are as high as, or higher than, that in established breast cancer cell lines treated with 1,25-dihydroxyvitamin D-3. These data confirm the association between CYP24 and breast cancer, supporting the use of CYP24 as a breast cancer marker in humans. The Examiner has acknowledged this point. Applicants have tailored the claims to be commensurate with Applicants' demonstrated association between CYP24 and breast cancer.

Accordingly, Applicants submit that the specification fully enables the pending claims. Withdrawal of the § 112 rejection for lack of enablement is therefore respectfully requested.

Conclusion.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 267-4160.

Any required fees accompany this response; if the amount of such fees is incorrect, please charge any required fees, or credit any overpayments, to Deposit Account No. 504480 (Order No. UCOTP089US).

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Respectfully submitted,

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